What is claimed is:

1. A method of comparing the phosphorylation states of one or more proteins in two or more samples comprising:

providing a substantially chemically identical and differentially isotopically labeled protein reactive reagent for each sample wherein the protein reactive reagent satisfies the formula:

CR-B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent (CR), L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated;

reacting each sample with one of the protein reactive reagents to provide proteins bound to the protein reactive reagent, whereby such bound proteins are differentially labeled with stable isotopes;

capturing bound proteins of the samples using the capture reagent that selectively binds the binding agent;

releasing captured bound proteins from the capture reagent by disrupting the interaction between the binding agent and the capture reagent; and

detecting the released bound proteins.

2. The method of claim 1, wherein the bound proteins in the samples are enzymatically or chemically processed to convert them into bound peptides.

3. The method of claim 1, wherein a protein portion of one or more of the bound proteins are sequenced by tandem mass spectrometry to identify the bound protein.

4. The method of claim 1, wherein the amount of one or more phosphorylated proteins in the sample is determined by mass spectrometry and further comprising introducing into a sample a known amount of one or more internal standards for each protein to be quantified.

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5. The method of claim 1, wherein one or more phosphorylated amino acid residues are selected from the group consisting of threonine, serine, and tyrosine.

6. The method of ~~claim 1,~~ wherein the released bound proteins are separated by chromatography prior to detecting the bound proteins by mass spectrometry.

claim 1 requires 72 samples

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7. The method of claim 1, wherein a plurality of proteins in a single sample are detected and identified.

8. The method of claim 3, wherein all of the proteins in a sample are identified.

>2 req'd

9. The method of claim 1, wherein relative amounts of one or more proteins in two or more samples are determined and further comprising combining differentially labeled samples, capturing bound proteins from the combined samples and measuring relative abundances of the bound proteins differentially labeled proteins.

10. The method ~~of claim~~ 1, wherein the proteins being quantified are membrane proteins.

11. The method of claim 1, wherein different samples contain proteins originating from different organelles or different subcellular fractions.

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12. The method of claim 9, wherein different samples represent proteins expressed in response to different environmental or nutritional conditions, different chemical or physical stimuli or at different times.

13. The method ~~of claim~~ 1, wherein the different samples represent proteins expressed in different disease states.

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14. A method for screening for a therapeutic that alters a phosphorylation state of a protein, the method comprising:

contacting at least one test sample containing the protein with the therapeutic;

providing at least one control sample containing the protein;

removing one or more phosphate groups from one or more amino acid residues of the protein in the at least one test sample and the at least one control sample; remove the same PO_4^{-3} groups

tagging the at least one test sample and the at least one control sample with substantially chemically identical and differentially isotopically labeled protein reactive reagents for each sample, wherein the protein reactive reagents satisfies the formula:

B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated; and

detecting a level of phosphorylation of the tagged proteins in the at least one test sample and the at least one control sample; and

determining whether the therapeutic altered the level of phosphorylation of the tagged proteins in the at least one test sample.

15. A reagent for mass spectrometric analysis of proteins that satisfies the general formula:

B-L-PhRG

where B is a binding agent that selectively binds to a capture reagent, L is a linker group that comprises at least one isotopically heavy atom and a phosphorylation reactive group (PhRG) that selectively labels proteins at one or more residues that were formerly occupied by phosphate groups.

16. The reagent of claim 15, wherein PhRG is selected from the group consisting essentially of primary amines, secondary amines, tertiary amines,

lactams, amides, imides, hydroxylamines, hydrazides, hydrazines, sulfites, sulfinates, sulfonamides, and mixtures thereof.

17. The reagent of claim 15 wherein the isotopically heavy atom is selected from the group consisting of ^{2}H, ^{13}C, ^{15}N, ^{17}O, ^{18}O, and ^{34}S.

18. The reagent of claim 15, wherein the reagent is soluble in a liquid protein sample.

19. The reagent of claim 15, wherein the linker is a cleavable linker.

20. The reagent of claim 15, wherein the binding agent is biotin or a modified biotin.

21. The reagent of claim 15, wherein the binding agent is selected from a group consisting essentially of a 1,2-diol, glutathione, maltose, a nitrilotriacetic acid, or an oligohistidine.

22. The reagent of claim 15, wherein the affinity label is a hapten.

23. A reagent for mass spectrometric analysis of proteins that satisfies the general formula:

$B\text{-}B^{1}\text{–}X^{1}\text{-}(CH_2)n\text{-}[X^{2}\text{-}(CH_2)m]_x\text{-}X^{3}\text{-}(CH_2)p\text{-}X^{4}\text{-}B^{2}\text{-}PhRG$

where: B is a binding agent, PhRG is a phosphate reactive group, $B^{1}\text{–}X^{1}\text{-}(CH_2)n\text{-}[X^{2}\text{-}(CH_2)m]_x\text{-}X^{3}\text{-}(CH_2)p\text{-}X^{4}\text{-}B^{2}$ is a linker group, wherein: X^{1}, X^{2}, X^{3} and X^{4}, are independently selected from a group consisting essentially of O, S, NH, NR, $NRR^{1}+$, CO, COO, COS, S-S, SO, SO_2, CO-NR, CS-NR^{1}, Si-O, aryl or diaryl, wherein at least one of the X^{1}, X^{2}, X^{3} and X^{4} groups comprises an isotopically heavy atom.

24. A method of detecting more than one type of phosphorylated amino acid residue in a protein, the method comprising:

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removing the phosphate group from at least one serine residue or at least one threonine residue;

removing the phosphate group from at least one tyrosine residue;

tagging the at least one serine residue or the at least one threonine residue with substantially chemically identical and differentially isotopically labeled protein reactive reagents for each sample, wherein the protein reactive reagents satisfies the formula:

B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated;

tagging the at least one tyrosine residue with substantially chemically identical and differentially isotopically labeled protein reactive reagents for each sample, wherein the protein reactive reagents satisfies the formula:

B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated; and

detecting the tagged protein.

25. The method of claim 24, wherein the removing the phosphate group from at least one serine residue or at least one threonine residue is after the removing the phosphate group from at least one tyrosine residue.

26. The method of claim 24, wherein tagging the at least one serine residue or the at least one threonine residue is done after the tagging the at least one tyrosine residue.

27. The method of claim 26, wherein the removing the phosphate group from at least one serine residue or at least one threonine residue is after the removing the phosphate group from at least one tyrosine residue.